

Preliminary Amendment to the claims 10/037,718 Applicants
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Remarks

Claims 1-90 have been canceled; new claims 91-139 read on the elected oligonucleotide invention. **These 49 new claims are, however, equivalent to only 23 claims: 1 independent claim, 20 dependent claims and 2 multiple dependent claims.** That is, of these 49 new claims, only 21 of these new claims (claims 91-111) have various combinations of limitations. The other 28 claims, claims 112-139, are further limited by only a single limitation that is the same limitation for claims 112-123 and for claims 124-139. **Therefore each of the two groups of claims, claims 112-123 and 124-139, is equivalent to a single multiple dependent claim.** That is, the new elected claims have essentially been grouped into 3 groups for convenience.

Also pending are 27 new claims that are not drawn to the elected invention. These 27 new claims are similar to previously pending process and apparatus claims.

Support for the new amended elected claims

The applicants will now cite some example support text in the application for the new amended claims. As stated in MPEP 2163.02: "*Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'*" The Examiner is urged to read the Abstract, Background paragraphs [0019]-[0029], [0034]-[0035], [0040]-[0042] and paragraphs [0046]-[0052] for a brief introduction to the invention. Some of the inventor Ralph McGinnis's published papers are cited in paragraphs [0027] and [0029].

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Remarks Summary: The Remarks for independent claim 91 and first dependent claim 92 are introductory and therefore consequently detailed. The Remarks for the subsequent claims 93 – 139 require much less detail and are much briefer. **These Remarks are lengthy because supporting text from the application is reproduced below. Some underlining and highlighting is also added for the Examiner's convenience.** For an overview of support for the elected oligonucleotide composition invention, see paragraphs [0264]-[0266] and related paragraphs [0254]-[0255] and Oligonucleotide Technology [0244]-[0249]. (Greater detail is in [0250]-[0253], [0256]-[0263].) For an overview of Systematic Covering, see [0049], [0052]; with more detailed support for Systematic Covering in [0079] (the term "gene" means trait-causing/determining polymorphism) and [0177]-[0185].

Regarding support for claim 91 for the clause "A composition, comprising: one or more copies of a set of oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers, wherein the group of covering markers is chosen so that a CL-F region is systematically covered by the covering markers".

Example support text:

[0264] Composition of Matter: Description of Comp set#1D [0265]
Comp set#1D: One or more copies of a set of oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers, wherein the group of covering markers systematically cover a CL-F region.

[0152] a) choosing two or more bi-allelic covering markers so that a CL-F region is systematically covered by the two or more covering markers;

For the clause "the covering markers and the CL-F region being for a species of creatures".

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Example support text:

- [0175]The CL-F region and covering markers are for a species

[0151]a species of creatures

For the clause "the CL-F region being a collection of one or more points on a two-dimensional CL-F map that is similar to an x-y graph,"

Example support text:

[0046] Versions of the present invention make use of the novel concept of systematically covering a region on a two-dimensional map similar to an x-y graph with bi-allelic markers. The x axis on this map is the chromosomal location dimension and the y axis of the map is the least common allele frequency dimension. This two-dimensional map is called a CL-F map in this application. (CL stands for chromosomal location and F stands for least common allele frequency.)

[0050] A region on a CL-F map is called a CL-F region. A CL-F region is a collection of one or more CL-F points.

For the clause "the CL-F map having the two orthogonal dimensions of chromosomal location (CL) and least common allele frequency (F)," see [0046] and [0050] just above and support text just below.

Example support text:

Abstract

.... marker distribution over a two-dimensional region having the orthogonal dimensions of chromosomal location and least common allele frequency.

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For the clause "wherein the group of covering markers comprises thousands of bi-allelic markers,"

Example support text:

[0249] Companies like Affymetrix are using high density arrays of oligonucleotides attached to silicon chips or glass slides to genotype DNA from one individual at thousands of bi-allelic markers.⁸

For the clause "wherein there are covering markers with least common allele frequencies less than or equal to 0.3" see example support text below and also Table 2 paragraph [0289], wherein P_t values for "m", marker least common allele frequency are given; in some examples m equals 0.3.

Example support text:

[0035]the inventor's calculations and observations indicate that bi-allelic markers having least common allele frequencies less than 0.3, 0.2 or even less than 0.1 have an important place in linkage studies using association based linkage tests. This is markedly different than Kruglyak's information content evaluation of bi-allelic markers for use in linkage studies, in which bi-allelic markers with least common allele frequencies less than 0.3 or 0.2 are viewed unfavorably.¹

[0293] Example Illustrating the Importance of Marker Heterozygosity (i.e. Allele Frequency)

[0294] To illustrate the importance of marker heterozygosity and disequilibrium, Table 2 shows P_t .. valuesan individual line in the table represents constant marker heterozygosity (m=0.5, 0.3, 0.2, or 0.1)

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Regarding support for claim 92 for the clause “.. wherein each oligonucleotide in the set is a type (1) complementary oligonucleotide or wherein each oligonucleotide in the set is a type (2) complementary oligonucleotide,

Example support text:

[0142] An allele is identified by a hybridization reaction with an oligonucleotide that is complementary to the allele. In this application there are two types of oligonucleotides that are complementary to an allele. The two types of oligonucleotides complementary to an allele are identified as type(1) or type(2).

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[0143] A type (1) complementary oligonucleotide is complementary to the part of an allele's DNA sequence that actually contains the allele's polymorphic site; and the type(1) complementary oligonucleotide has utility to identify the allele by means of a hybridization reaction of the oligonucleotide to the part of the allele's DNA sequence that actually contains the allele's polymorphic site. A hybridization reaction of a type(1) oligonucleotide to the part of an allele's DNA sequence that actually contains the allele's polymorphic site is a type (1) hybridization reaction. A type (2) complementary oligonucleotide is complementary to an allele at a DNA sequence that flanks (but does not contain) the allele's polymorphic site; and the type (2) complementary oligonucleotide has utility to identify the allele by means of a hybridization reaction wherein the oligonucleotide hybridizes to the allele at a DNA sequence that flanks (but does not contain) the allele's polymorphic site and identification of the allele is subsequently achieved by extension of the oligonucleotide (and possibly one or more other type(2)complementary oligonucleotides) across the polymorphic site with a DNA polymerase such as occurs, for example, in a standard PCR (polymerase chain reaction).

For the clause "wherein the CL-F region is for the species of creatures and for a population,"

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Example support text:

[0175] The CL-F region and covering markers are for a species The chromosomal location coordinate of each covering marker is based on information regarding the chromosomal location of each covering marker. One such source of information is chromosomal maps. Chromosomal maps are provided by such institutions as the Whitehead Institute or Marshfield Foundation for Biomedical Research

[0176] The least common allele frequency coordinate of each covering marker is based on any reasonable information regarding the least common allele frequency of each covering marker. It is possible to use information from different populations for the allele frequencies of different covering markers. For example, it is possible for the least common allele frequencies of two different covering markers to be based on information from two different, but similar populations. For purposes of technical convenience, the least common allele frequency of each covering marker is based on information from the same population. One source of information on least common allele frequency is institutions which provide chromosomal maps such as the Whitehead Institute or Marshfield Foundation for Biomedical Research.

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For the clause "wherein the population is a population as in the field of population genetics," see text from bottom [0135] (the term population is used in a statistical sense and in the sense the term population is used in the field of population genetics). See also [0306] the term population here is used as in the field of population genetics (e.g., Finnish populations).

Example support text:

[0135]The term population in this application is not used purely in the sense the term population is used in the field of population genetics.

[0306]based on chromosomal maps such as those provided by the Whitehead Institute or Marshfield Foundation for Biomedical Research. Although disequilibrium has been observed in Finnish populations between polymorphisms that are 7 to 10 centimorgans (cM) apart

For the clause "wherein the CL-F region is N covered to within [x, y] by the two or more bi-allelic covering markers, wherein [x, y] is a two-dimensional distance," CL-F distances are two-dimensional and represented, for example, as [x, y] or as [δ_{CL} , δ_F], see [0048] below.

Example support text:

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[0048] Distances between any two CL-F points on a CL-F map are given in terms of two numbers: chromosomal location distance and frequency distance. The first number is the distance in the horizontal, chromosomal location direction. This first number is the chromosomal location distance. The second number is the distance in the vertical, frequency direction. This second number is the frequency distance. For example, the CL-F distance δ is given by two numbers δ_{CL} (chromosomal location distance) and δ_F (frequency distance). This is represented as $\delta = [$ $\delta_{CL}, \delta_F]$.

[0049] The "clustering" of bi-allelic markers near a particular CL-F point is discussed in terms of the number of markers within a particular CL-F distance of the point. For example, if each of N bi-allelic markers is separated from the point by a CL-F distance of less than or equal to δ , then the point is said to be N covered by the markers to within the distance δ (N being an integer number.)

For support for the clause "wherein x is less than or equal to about D_{CL} or the equivalent thereof,..... D_{CL} is equal to the largest chromosomal length, computed by any method, for which linkage disequilibrium has been observed between any polymorphisms in any population of the species,"

Example support text:

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[0178] In this application, the systematic covering of a CL-F region in versions of the invention is described mathematically as the covering of a CL-F region, wherein the CL-F region is N covered to within a CL-F distance δ by two or more bi-allelic covering markers. The covering markers are chosen so that the CL-F region is N covered to within the CL-F distance δ

[0179] It is possible for the chromosomal location component of δ to be as great as about any chromosomal length, computed by any method, for which linkage disequilibrium has been observed between any polymorphisms in any population of the species.

For support for the clause "and y is less than or equal to about 0.2".

Example support text:

[0180] It is possible for the frequency distance component of δ to be as great as about 0.2.

For support for the clause "N is an integer greater than or equal to 1"

Example support text:

Definitions

[0080] If a CL-F region is said to be N covered to within a CL-F distance δ by one or more covering markers then each point in the region is N covered to within the CL-F distance δ by the one or more covering markers. Wherein N is an integer greater than or equal to one.

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[0267] Example 1Comp: one or more copies of a set of oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers, a CL-F region being N covered by the covering markers to within a CL-F distance of about [1 cM, 0.2] or the equivalent thereof, wherein N is an integer greater than or equal to one.

Regarding support for claim 93 and the clause "wherein x is less than about D_{CL} "

Example support text:

[0179] It is preferable in terms of increasing the power of a version of the invention for linkage studies that the chromosomal location component of δ be less than about the greatest chromosomal length, computed by any method, for which linkage disequilibrium has been observed between any polymorphisms in any population of the species.

Regarding support for the clause "wherein each oligonucleotide in the set is a type (1) complementary oligonucleotide that is allele specific and each covering marker is an SNP", type (1) allele specific complementary alleles are generally used to identify SNPs in oligonucleotide arrays".

Example support text:

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[0249] Companies like Affymetrix are using high density arrays of oligonucleotides attached to silicon chips or glass slides to genotype DNA from one individual at thousands of bi-allelic markers.¹ In some of these versions of oligonucleotide technology, the strength of hybridization of oligonucleotides that differ at only one base to DNA containing an SNP are compared to determine genotype.²

[0324] Companies like Affymetrix³ are using silicon chips or glass slides to genotype DNA from one individual at thousands of bi-allelic markers. To the surface of each cell is attached multiple copies of a unique oligonucleotide whose sequence is complementary (type (1)) to one of the two alleles of a particular bi-allelic marker.

Regarding support for claim 94, support for the limitations in this claim have been discussed above, except for the clause "*x is less than or equal to about 10 to 12 cM*". For this clause, see paragraph [0181].

Example support text:

[0181] Linkage disequilibrium has been observed between polymorphisms separated by 10 to 12 cM in some homogeneous human populations. Therefore, it is possible for the chromosomal location distance component of δ to be as large as about 10 to 12 cM, about 10 to 12 million bp, or the equivalent thereof

Regarding support for claim 95, support for the clause "*wherein y is less than or equal to 0.2*", as stated above the two-dimensional CL-F covering distance is represented as [x, y] or as [δ_{CL} , δ_F], y or δ_F is the frequency component of the covering distance, see above under Remarks for claim 92. See paragraph [0180].

Example support text:

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[0180] It is possible for the frequency distance component of δ to be as great as about 0.2. (Depending on the penetrance ratio (r) or the disequilibrium between marker and gene, it is also possible for the frequency distance component of δ to be greater than 0.2 under some conditions as evidenced by Table 2 under Theory of Operation.

Regarding support for claim 96, support for the clause "*wherein there are covering markers with least common allele frequencies less than 0.2*" see text below and examples for "m" (model marker least common allele frequency) of 0.1 and 0.05 in Table 2, [0289].

Example support text:

[0035]the inventor's calculations and observations indicate that bi-allelic markers having least common allele frequencies less than 0.3, 0.2 or even less than 0.1 have an important place in linkage studies using association based linkage tests. This is markedly different than Kruglyak's information content evaluation of bi-allelic markers for use in linkage studies, in which bi-allelic markers with least common allele frequencies less than 0.3 or 0.2 are viewed unfavorably.⁴

Regarding support for claim 97, support for the clause "*wherein there are covering markers with least common allele frequencies less than 0.1*" see comments just above under claim 96.

Regarding support for claim 98, support for the clause "*wherein x is less than or equal to about 1 million base pairs*" see text below and examples in [0223] and [0267] (1 million base pairs is equivalent to 1 cM.)

Example support text:

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[0181] It is preferable in terms of increasing the power of a version of the invention for linkage studies in human populations that δ is less than or equal to about [1 million bp, 0.15] or the equivalent thereof.

Regarding support for claims 99 and 100 see comments above under claims 96 and 97.

Regarding support for claim 101 and the clause "*wherein x is less than or equal to 250,000 base pairs*" see examples in [0192] and [0263] and text below.

Example support text:

[0181] It is more preferable in terms of increasing the power of a version of the invention for linkage studies in human populations that δ is less than or equal to about [250,000 bp, 0.1] or the equivalent thereof.

Regarding support for claims 102 and 103 see comments above under claims 96 and 97.

Regarding support for claim 104 CL-F regions are described in [0050] and [0075], segment-subranges are rectangular CL-F regions, see [0089] to [0095]. A CL-F region bounded by a chromosomal segment that is the length of a chromosome and by the subrange 0 to 0.5 is the largest CL-F region that is confined to the chromosome.

Example support text:

[0089] A segment-subrange pair is the pair formed by pairing a segment of a chromosome and a subrange of the least common allele frequency range 0 to 0.5.

[0090] The term segment-subrange is used as a short version of the term segment-subrange pair. (A segment-subrange is a rectangular region on a CL-F map or a rectangular CL-F region, see below.)

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[0183] In general, the larger the CL-F region which is N covered, the greater the power of a version of the invention for linkage studies, because a larger region is scanned (covered).

[0185] Specific types of CL-F regions that are N covered are useful. For example, a rectangular CL-F region, a segment-subrange, that is N covered is used in an association based linkage study to test for the presence of a trait causing bi-allelic gene located within the segment-subrange.

Regarding support for claim 105 and the clause "*wherein x is less than or equal to 250,000 base pairs*" see comments above under claim 101.

Regarding support for claim 106 and the clause "*wherein N is greater than 2*", in general greater values of N are preferred, see text below and see examples from [0192] and [0263] "*wherein N is an integer number greater than or equal to 2*" below. The greater alternative, N greater than 2, is thus supported; see text below. See also example from [

Example support text:

[0182]In general, the greater N is, the greater the power of a version of the invention for linkage studies. Because the greater N is, the greater the chance that linkage is detected between one or more covering markers and a gene or genes.

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[0192] a) choosing two or more bi-allelic covering markers so that a CL-F region is N covered to within a CL-F distance [250,000 bp, 0.1] or the equivalent thereof by the covering markers, wherein N is an integer number greater than or equal to 2;

[0263] The use in genotyping one or more individuals, of one or more copies of a set of oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers, a CL-F region being N covered by the covering markers to within a CL-F distance of about [250,000 bp, 0.1] or the equivalent thereof, wherein N is an integer greater than or equal to two.

For support in claim 106 for the clause "the species is human being and the chromosome is any one of human chromosomes 1-6", see text below regarding CL-F regions and specific human chromosomes.

Example support text:

[0075] A CL-F region is a group of CL-F points. A CL-F region is a region that is or can be represented on a CL-F map. A particular CL-F region may be large or small. For example the chromosomal location coordinates of CL-F points in a particular CL-F region can range over an entire chromosome (for example human chromosome number 6). Alternatively the chromosomal location coordinates of CL-F points in a particular CL-F region can range over more than one chromosome, for example all the human chromosomes, human chromosomes numbers 1 through 22 and X and Y.

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For support for claim 107 see comments above under claim 106. For support for the clause "y is 0.1", as noted above the frequency component of the covering distance δ is represented as y or δ_F , see Remarks under claims 92 and 95; and see text below.

Example support text:

[0181] It is more preferable in terms of increasing the power of a version of the invention for linkage studies in human populations that δ is less than or equal to about [250,000 bp, 0.1] or the equivalent thereof.

[0192] a) choosing two or more bi-allelic covering markers so that a CL-F region is N covered to within a CL-F distance [250,000 bp, 0.1] or the equivalent thereof by the covering markers, wherein N is an integer number greater than or equal to 2;

[0263] The use in genotyping one or more individuals, of one or more copies of a set of oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers, a CL-F region being N covered by the covering markers to within a CL-F distance of about [250,000 bp, 0.1] or the equivalent thereof, wherein N is an integer greater than or equal to two.

For support for claim 108 see comments above under claim 104. The length of a chromosomal segment can be as great as an entire chromosome.

Example support text:

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[0275] The chromosomal location axis of each graph spans the chromosomal locations on one or more segments of one or more chromosomes of a species, each of the one or more segments is a size from the equivalent of a base pair in length to the length of an entire chromosome (or the equivalent thereof).

For support for the clause in claim 108 "wherein the subrange of the segment-subrange is the subrange 0 to less than 0.1". See [0311] below (from the Theory of Operation/Set/Subset Example [0281], [0301]) which describes the desirability of covering bi-allelic allele frequencies below "0.1/above 0.9". Bi-allelic allele frequencies "0.1/above 0.9" is equivalent to the least common allele frequency subrange 0 to less than 0.1. (See also [0075] which says, "*the least common allele frequency coordinates of CL-F points in a particular CL-F region can range over only a very small subrange*" and gives an example of a subrange (the subrange 0.1 to 0.2) of small width (0.1). This width, 0.1, is the same as the width of the subrange 0 to less than 0.1.)

Example support text:

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[0311] Therefore, in searching for association-based linkage to a bi-allelic disease locus within each of the aforementioned chromosomal segments (see step 1), it is crucial to identify and test (e.g., by TDT) bi-allelic markers within each segment that have a broad range of allele frequencies. **An unidentified bi-allelic disease locus could have allele frequencies close to 0.5/0.5, 0.4/0.6, 0.3/0.7, 0.2/0.8, 0.1/0.9 or below 0.1/above 0.9; hence, it is crucial to test bi-allelic markers with frequencies near 0.5/0.5 and near 0.1/0.9 as well as test others with allele frequencies that fall at regular increments between the extremes of 0.5/0.5 and 0.1/0.9.** By testing bi-allelic markers with a broad range of allele frequencies that are spaced at regular intervals between 0.5/0.5 and 0.1/0.9, one is assured of testing some bi-allelic markers whose two allele frequencies are reasonably close to the allele frequencies of an unknown bi-allelic disease locus.

For support for claim 109, see comments above under claim 101.

For support for claim 110, support for the limitations beginning with "*wherein the CL-F region is for a species and a population*" is cited above under claims 91 and 92, "*wherein the species is human being*" is cited under claim 106 and is present throughout the application, e.g. Abstract. Support for "*wherein the population is a population as in the field of population genetics*" is cited under claim 92; support for "*each oligonucleotide in the set is a type (1) complementary oligonucleotide that is allele specific and each covering marker is an SNP*" is cited above under claim 92.

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For the remaining limitations in the claim, see, e.g. [0160], [0220], [0237] i.e. "*any method of systematically covering the CL-F region is acceptable*". Such a method is taught in detail in the Set/Subset Example paragraphs [0301] through [0321] inclusive of the Theory of Operation/Set/Subset Example [0281]. **Some excerpts from the text are given below.** In this Set/Subset Example, a CL-F region is systematically covered using covering markers that are members of sets and subsets. Marker set and subset membership is based on the markers being located on particular chromosomal segments and having a particular least common allele frequencies.

Each of the whereby clauses in this claim merely states the result of the invention recited in the claim and is not a limitation. As stated by the Federal Circuit, "[a] 'whereby' clause that merely states the result of limitations in the claim adds nothing to the patentability and substance of the claim." Texas Instruments, Inc. v. U.S. Int'l Trade Commission, 988 F 2d 1165, 1172, 26 USPQ2d 1018, 1023 (Fed. Cir. 1993).

Example support text:

[0160] a) choosing two or more bi-allelic covering markers so that a CL-F region is systematically covered by the two or more covering markers; **Any method of systematically covering the CL-F region is acceptable.**

[0281] Theory of Operation/Set/Subset Example

[0301] Set/Subset Example

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[0306] first divide the chromosome or subregion of interest into segments that are short enough that polymorphisms within each segment are likely to be in linkage disequilibrium with each other. These chromosomal segments might or might not overlap each other (i.e., share some of their length in common); but the set of chromosomal segments should completely cover the entire chromosome or entire subregion of interest,

[0312] within each chromosomal segment, subsets of bi-allelic markers should be identified. Each subset contains only bi-allelic markers having approximately the same allele frequencies. For example, subset A contains only markers whose less common allele has a population frequency of about 0.1. Similarly, subsets B, C, D, and E contain only bi-allelic markers whose less common allele has a frequency of approximately 0.2, 0.3, 0.4, and 0.5, respectively. In other versions of the invention the number of subsets is greater or less than five,..... However, the crucial point is that each subset should contain only bi-allelic markers belonging to one chromosomal segment and the frequency of the less common allele of each subset member should be approximately the same (i.e., the difference between the frequencies of the less common allele of any two subset members should not exceed 0.15). Also crucial, as I emphasized above, is that the group of subsets for each chromosomal segment represent frequencies near the extremes of 0.5/0.5 and 0.1/0.9 as well as represent bi-allele frequencies between these two extremes that are approximately evenly spaced as illustrated by the group of subsets referred to above as A, B, C, D and E.

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[0321] In this set/subset example, the least common allele frequency subrange 0.1 to 0.5 is used. In versions of the invention similar to the set/subset example, versions of the invention are operable and have utility for any subrange of the least common allele frequency range 0 to 0.5.

For support for claim 111 for the limitations "*wherein an apparatus comprises copies of the set of oligonucleotides, wherein the apparatus comprises a high-density oligonucleotide array and the array comprises copies of the set of oligonucleotides; or wherein the apparatus comprises a glass slide and the oligonucleotides are attached to the glass slide; or wherein the apparatus comprises a silicon chip and the oligonucleotides are attached to the silicon chip*" see [0249], [0324], [0341].

Example support text:

[0249] Companies like Affymetrix are using high density arrays of oligonucleotides attached to silicon chips or glass slides to genotype DNA from one individual at thousands of bi-allelic markers.*

[0341] *Accessing Genetic Information with High-Density DNA Arrays, Mark Chee, et al. Science, vol 274, Oct. 25, 1996, pp. 610-614.

For support for claims 112-123, see Remarks above under claim 111.

For support for claims 124-139 for the limitation "*wherein the species is human being*" see Remarks under claim 106. The species human being is described throughout the application, see for example the Abstract, [003], [0012], [0066], and [0191].

Further Remarks

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No supporting Remarks for the non-elected claims are given here as the applicants respectfully submit that in general the non-elected independent claims are generally supported verbatim by the application, have limitations that are similar to the limitations in the elected claims, or have associated Remarks in previous Responses. The applicants hereby rebut any presumption of surrender of equivalents of oligonucleotides attached to a silicon chip, glass slide or part of an array.

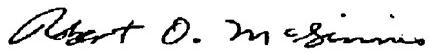
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Conclusion

Claims 1-90 have been canceled; new claims 91-139 read on the elected oligonucleotide invention. These 49 new claims are, however, equivalent to only 23 claims: 1 independent claim, 20 dependent claims and 2 multiple dependent claims. Remarks have been respectfully submitted. Also pending are 27 new claims that are not drawn to the elected invention. These 27 new claims are similar to previously pending process and apparatus claims. Seventy-six claims (including 7 independent) are now pending unchanged from previously, no extra claim fee is due.

For the reasons advanced above, applicants respectfully submit that the claims are now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,



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